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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

ZHUO, Xiula

Serial No. 10/039,761

Filed: October 19, 2001

For: *Modulators Of Leukocyte Activation, Compositions And Methods Of Use*

Examiner: UNKNOWN

Group Art Unit: 1623

CERTIFICATE OF MAILING
I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, BOX SEQUENCE, P.O. BOX 2327, Arlington, VA 22202 on:
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PRELIMINARY AMENDMENT RE SEQUENCE LISTING

Commissioner for Patents
U.S. Patent and Trademark Office
BOX SEQUENCE, P.O. Box 2327
Arlington, VA 22202

Sir:

This Amendment is in response to the Notice to File Missing Parts of Nonprovisional Application mailed April 9, 2002. A copy of the notice is enclosed herewith. Please amend the application as follows to comply with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures in adherence with rules 37 C.F.R. § 1.821-1.825:

IN THE SPECIFICATION:

Please replace paragraph beginning at page 11, line 26, with the following rewritten paragraph:

— Figure 5 shows domain analysis of the amino acid sequence of SUP protein (SEQ ID NO:5). The cysteine residue which is characteristic of ubiquitin specific protease domains is enlarged and bolded. The two conserved histidine residues that are characteristic of ubiquitin specific protease domains are enlarged.—

Please replace paragraph beginning at page 12, line 2, with the following rewritten paragraph:

— Figure 9 (top) shows domain analysis of the amino acid sequence of SUP protein (SEQ ID NO:5). The protein sequence is broken down into the ubiquitin-associated domain, the ubiquitin protease domain, and the response regulatory domain. The catalytic cysteine active site with a conserved cysteine residue which is characteristic of ubiquitin specific protease domains is indicated. The PKC site is indicated. The tyrosine phosphorylation site is indicated. The active site conserved histidines characteristic of ubiquitin specific protease domains are indicated.—

Please replace paragraph beginning at page 15, line 8, with the following rewritten paragraph:

— In a preferred embodiment, the USP-25 protein comprises the amino acid sequence set forth in SEQ ID NO:2 or 4. In a preferred embodiment, the USP-25 protein comprises a fragment of the amino acid sequence set forth in SEQ ID NO:2 or 4 and comprises a ubiquitin-specific peptidase domain. The characteristics described below can apply to any of the USP-25 proteins provided herein.—

On page 69, immediately preceding the heading "CLAIMS", please insert the enclosed text entitled "SEQUENCE LISTING".

IN THE CLAIMS:

Please enter the following replacement claim set:

— 1. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin-like protein, and a candidate bioactive agent; and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent; wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 2 (SEQ ID NO:2), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.

2. The method according to Claim 1 wherein said USP-25 target protein is selected from the group consisting of UBC9, SYK and calcineurin.

3. The method according to Claim 1, wherein said ubiquitin-like protein is SMT3/SUMO or NEDD8/RUBY.

4. (Amended) The method according to Claim 1, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 2 (SEQ ID NO:2).

5. (Amended) The method according to Claim 1, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to a fragment of the full

length amino acid sequence set forth in Figure 2 (SEQ ID NO:2) wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

6. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin-like protein, and a candidate bioactive agent; and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent; wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 4 (SEQ ID NO:4), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.

7. The method according to Claim 6, wherein said USP-25 target protein is selected from the group consisting of UBC9, SYK and calcineurin.

8. The method according to Claim 6, wherein said ubiquitin-like protein is SMT3/SUMO or NEDD8/RUBY.

9. (Amended) The method according to Claim 6, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 4 (SEQ ID NO:4).

10. (Amended) The method according to Claim 6, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to a fragment of the full

length amino acid sequence set forth in Figure 4 (SEQ ID NO:4) and wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

11. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin-like protein, and a candidate bioactive agen;t and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent; wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 1 (SEQ ID NO:1), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.

12. The method according to Claim 11, wherein said USP-25 target protein is selected from the group consisting of UBC9, SYK and calcineurin.

13. The method according to Claim 11, wherein said ubiquitin-like protein is SMT3/SUMO or NEDD8/RUBY.

14. (Amended) The method according to Claim 11, wherein said USP-25 protein comprises the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 1 (SEQ ID NO:1).

15. (Amended) The method according to Claim 11, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to an amino acid sequence

encoded by a fragment of the full length nucleic acid sequence set forth in Figure1 (SEQ ID NO:1), wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

16. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin like protein, and a candidate bioactive agent; and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 3 (SEQ ID NO:3), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.

17. The method according to Claim 16, wherein said USP-25 target protein is selected from the group consisting of UBC9, SYK and calcineurin.

18. The method according to Claim 16, wherein said ubiquitin-like protein is SMT3/SUMO or NEDD8/RUBY.

19. (Amended) The method according to Claim 16, wherein said USP-25 protein comprises the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 1 (SEQ ID NO:1).

20. (Amended) The method according to Claim 16, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to an amino acid sequence

encoded by a fragment of the full length nucleic acid sequence set forth in Figure1 (SEQ ID NO:1), wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

21. (Amended) A method for screening for a bioactive agent capable of modulating lymphocyte activation, comprising:

i) contacting a candidate bioactive agent to a lymphocyte comprising a recombinant nucleic acid encoding a USP-25 protein;

ii) inducing activation of said lymphocyte; and

iii) determining the activation of said lymphocyte in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 2 (SEQ ID NO:2), and wherein a difference in the activation of said lymphocyte in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating lymphocyte activation.

22. (Amended) The method according to Claim 21, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 2 (SEQ ID NO:2).

23. The method according to Claim 21, wherein said determining the activation of said lymphocyte comprises determining the activity of the immunoglobulin heavy chain gene promoter or the nuclear factor in activated T cells (NFAT) gene promoter.

24. (Amended) A method for screening for a bioactive agent capable of modulating lymphocyte activation, comprising:

i) contacting a candidate bioactive agent to a lymphocyte comprising a recombinant nucleic acid encoding a USP-25 protein;

ii) inducing activation of said lymphocyte; and

iii) determining the activation of said lymphocyte in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 4 (SEQ ID NO:4), and wherein a difference in the activation of said lymphocyte in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating lymphocyte activation.

25. (Amended) The method according to Claim 24, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 4 (SEQ ID NO:4).

26. The method according to Claim 24, wherein said determining the activation of said lymphocyte comprises determining the activity of the immunoglobulin heavy chain gene promoter or the nuclear factor in activated T cells (NFAT) gene promoter.

27. The method according to Claim 23 or 26, wherein said determining the activation of said lymphocyte further comprises determining the expression of CD69.

REMARKS

The specification and claims have been amended to include a Sequence Listing and proper reference to the sequences therein and to correct minor typographical errors. A "clean" version of the now-pending claim set is provided above. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Entry of this amendment is respectfully requested. The amendments are made in adherence with 37 C.F.R. § 1.821-1.825. This amendment is accompanied by a floppy disk containing the above named sequence, SEQUENCE ID NUMBERS 1-5 in computer readable form, and a paper copy of the sequence information. The computer readable sequence listing was prepared through use of the software program "PatentIn" provided by the PTO. The information contained in the computer readable disk is identical to that of the paper copy. This amendment contains no new matter.

Applicant submits that this amendment, the accompanying computer readable sequence listing, and the paper copy thereof serve to place this application in a condition of adherence to the rules 37 C.F.R. § 1.821-1.825. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

Dated: 10/8/02

BY: Robin M. Silva

Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
Facsimile: (415) 398-3249

Robin M. Silva, Reg. No. 38,304
Filed under 37 C.F.R. § 1.34(a)

Serial No. 10/039,761
Filed: October 19, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at page 11, line 26, has been amended as follows:

— Figure 5 shows domain analysis of the amino acid sequence of SUP protein (SEQ ID NO:5). The cysteine residue which is characteristic of ubiquitin specific protease domains is enlarged and bolded. The two conserved histidine residues that are characteristic of ubiquitin specific protease domains are enlarged.—

Paragraph beginning at page 12, line 2, has been amended as follows:

— Figure 9 (top) shows domain analysis of the amino acid sequence of SUP protein (SEQ ID NO:5). The protein sequence is broken down into the ubiquitin-associated domain, the ubiquitin protease domain, and the response regulatory domain. The catalytic cysteine active site with a conserved cysteine residue which is characteristic of ubiquitin specific protease domains is indicated. The PKC site is indicated. The tyrosine phosphorylation site is indicated. The active site conserved histidines characteristic of ubiquitin specific protease domains are indicated.—

Paragraph beginning at page 15, line 8, has been amended as follows:

— In a preferred embodiment, the USP-25 protein comprises the amino acid sequence set forth in SEQ ID NO:2 ~~et~~ or 4. In a preferred embodiment, the USP-25 protein comprises a fragment of the amino acid sequence set forth in SEQ ID NO:2 or 4 and comprises a ubiquitin-specific peptidase domain. The characteristics described below can apply to any of the USP-25 proteins provided herein.—

On page 69, immediately preceding the heading "CLAIMS", the enclosed "SEQUENCE LISTING" was inserted into the specification.

IN THE CLAIMS:

The claims have been amended as follows. Only those claims with changes are included below.

—1. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin-like protein, and a candidate bioactive agent; and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 2 (SEQ ID NO:2), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.—

—4. (Amended) The method according to Claim 1, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 2 (SEQ ID NO:2).

5. (Amended) The method according to Claim 1, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to a fragment of the full length amino acid sequence set forth in Figure 2 (SEQ ID NO:2) wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

6. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin-like protein, and a candidate bioactive agent; and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent; wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 4 (SEQ ID NO:4), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.—

—9. (Amended) The method according to Claim 6, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 4 (SEQ ID NO:4).

10. (Amended) The method according to Claim 6, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to a fragment of the full length amino acid sequence set forth in Figure 4 (SEQ ID NO:4) and wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

11. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin-like protein, and a candidate bioactive agen;t and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 1 (SEQ ID NO:1), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.—

—14. (Amended) The method according to Claim 11, wherein said USP-25 protein comprises the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 1 (SEQ ID NO:1).

15. (Amended) The method according to Claim 11, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to an amino acid sequence encoded by a fragment of the full length nucleic acid sequence set forth in Figure1 (SEQ ID NO:1), wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

16. (Amended) A method for screening for a bioactive agent capable of modulating USP-25 protein activity, comprising:

a) combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin like protein, and a candidate bioactive agent; and

b) determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 3

(SEQ ID NO:3), wherein said USP-25 protein will bind to said USP-25 target protein, and wherein a difference in the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating USP-25 protein activity.—

—19. (Amended) The method according to Claim 16, wherein said USP-25 protein comprises the amino acid sequence encoded by the nucleic acid sequence set forth in Figure 1 (SEQ ID NO:1).

20. (Amended) The method according to Claim 16, wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to an amino acid sequence encoded by a fragment of the full length nucleic acid sequence set forth in Figure1 (SEQ ID NO:1), wherein said USP-25 protein comprises a ubiquitin-specific peptidase domain.

21. (Amended) A method for screening for a bioactive agent capable of modulating lymphocyte activation, comprising:

i) contacting a candidate bioactive agent to a lymphocyte comprising a recombinant nucleic acid encoding a USP-25 protein;

ii) inducing activation of said lymphocyte; and

iii) determining the activation of said lymphocyte in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 2 (SEQ ID NO:2), and wherein a difference in the activation of said lymphocyte in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating lymphocyte activation.

22. (Amended) The method according to Claim 21, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 2 (SEQ ID NO:2).—

—24. (Amended) A method for screening for a bioactive agent capable of modulating lymphocyte activation, comprising:

i) contacting a candidate bioactive agent to a lymphocyte comprising a recombinant nucleic acid encoding a USP-25 protein;

ii) inducing activation of said lymphocyte; and

iii) determining the activation of said lymphocyte in the presence and absence of said candidate bioactive agent;

wherein said USP-25 protein comprises an amino acid sequence having at least about 95% identity to the amino acid sequence set forth in Figure 4 (SEQ ID NO:4), and wherein a difference in the activation of said lymphocyte in the presence and absence of said candidate bioactive agent indicates that said candidate bioactive agent is capable of modulating lymphocyte activation.

25. (Amended) The method according to Claim 24, wherein said USP-25 protein comprises the amino acid sequence set forth in Figure 4 (SEQ ID NO:4).—